UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/036,063 | 12/26/2001 | Audrey Goddard | P3030R1C6 | 4326 |

30313 7590 01/27/2006

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

| EXAMINER | |
|---|---|
| KOLKER, DANIEL E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1649 | |

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) |
|---|---|---|
| | 10/036,063 | GODDARD ET AL. |
| | Examiner | Art Unit |
| | Daniel Kolker | 1649 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *22-26 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6/20/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

2. Applicant's remarks, amendments, and declarations filed 20 June 2005 have been entered. Claim 27 has been cancelled, new claims 28 – 30 have been added. Claims 22 – 26 and 28 – 30 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The deletion of inventors under 37 CFR 1.48(b) is acknowledged.

### *Information Disclosure Statement*

5. The information disclosure statement filed 20 June 2005 has been considered. The BLAST results indicate that applicants are aware of nucleic acids and proteins with identity or homology to the one claimed herein. However the results cannot be considered because there is no alignment provided, nor is there an indication of the percent identity between the claimed sequence and the reference sequences. Applicant states on p. 5 of the remarks that the newly-submitted documents include references to specific accession numbers and sequences. Applicant is advised that the BLAST results submitted appear to be a list of sequences which match, but do not provide either alignments or indications of how the sequences are related to the instantly-claimed peptides. Therefore the examiner cannot determine if the sequence accession numbers submitted by applicant constitute prior art. Furthermore the search results submitted appear to be the results are not publicly available documents. Applicant is directed to MPEP 609 and 37 CFR 1.97 and 1.98.

### *Withdrawn Objections and Rejections*

6. The following objections or rejections made in the previous office action are withdrawn:

The objections to the specification. Applicant has deleted the hyperlinks and changed the title.

The rejection of claims 22 - 27 under 35 USC 112, second paragraph. Applicant has cancelled the claim.

***Rejections Maintained***

***Claim Rejections - 35 USC §§ 101 and 112***

7. Claims 22 – 26 and 28 – 30 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The rejection is maintained for the reasons made of record in the previous office action and reiterated below.

The claims are drawn to antibodies which bind to SEQ ID NO:57, also called PRO4380. There is no asserted utility for antibodies which bind to PRO4380 independent from their utilities in purifying, detecting, or binding to PRO4380. For example, there is no contemplation of use of anti-PRO4380 antibodies as therapeutics in treating a specific disease. There is no disclosure of informative data on how purifying or detecting PRO4380 would be useful. An antibody that binds to a protein with a specific and substantial utility would itself be useful, as it could be used to purify that protein. An antibody could also be useful if it could be used to distinguish between patients with a disease and those free of disease, for example. However, in the instant case, the antibody has not been shown to be useful in the detection or treatment of disease or conditions, or in the purification of a protein that has utility. The utility of the antibodies hinges on whether or not PRO994 itself is useful.

The specification asserts that PRO4380 has two specific utilities, as it came up positive in two assays, however neither utility is substantial.

Applicant did not address the examiner's arguments that the first assay, Example 37 (page 166), drawn to compounds which test positive as either stimulators or inhibitors of glucose or FFA uptake, does not constitute a reasonable test for useful compounds. This assay is deemed to lack utility for the reasons made of record in the previous office action.

The data presented in Example 41 (p. 168 – 169) of the specification indicate that PRO4380 was positive in the Mouse Kidney Mesangial Cell Proliferation Assay. It is acknowledged that proliferation of mammalian kidney mesangial cells is useful, as Schocklmann (1999. Kidney International 56:1199-1207) teaches that such proliferation is necessary after injury or damage to the kidney. However, the threshold used in determining whether a particular PRO molecule counts as "positive" in this assay would not be considered reasonable by one of skill in the art. The specification discloses (p. 169, lines 1 – 2) that positives in this assay include anything which is at least 15% over the control reading. The post-filing

publication by Rovin et al. (2002. Kidney International 61:1293-1302) indicates that a 21% increase in human mesangial cell proliferation is not statistically significant (see particularly p. 1296, lines 3 – 6).

On page 6 of the remarks applicant refers to the utility guidelines on specific, substantial, and credible utilities. The claims were not rejected for lack of a specific or credible utility, thus arguments related to those (i.e page 6, points (1) and (3) in the final paragraph) are not germane. Particularly, the citation of MPEP 2107 II (B)(1)(ii), drawn to credible utilities is not on point as no rejection for lack of credibility was made.

On p. 7 of the remarks, applicant argues that utility need not be proven, that a reasonable correlation between the evidence and the asserted utility is sufficient, and that the asserted utility should be accepted if it is more likely than not true. Applicant cites *In re Langer*; *In re Jolles*, *In re Irons*, *In re Sichert*, *Raytheon v. Roper*, and *In re Oetiker* as supporting this argument. Applicant's arguments have been fully considered but are not persuasive.

In *In re Langer*, the court ruled the Patent Office cannot require clinical testing in humans to rebut a prima facie case for lack of utility. In the instant case, the Office has not made such a requirement. Furthermore the Langer court ruled that "Assuming that sufficient reason to question the statement of utility and its scope does exist, a rejection for lack of utility under § 101 will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the statement of utility and its scope as found in the specification are true." In the instant case there is in fact sufficient reason to question the statement of utility. The reference by Rovin cited in the previous office action indicates that the 15% threshold used by applicant is not reasonable. Therefore one of skill in the art would have reason to doubt the asserted utility.

In *In re Jolles*, the issue was whether data from an art-recognized animal model could be considered predictive of results in humans. That is not an issue in the instant case, as the examiner indicated in the paragraph spanning pp. 5 – 6 of the previous office action that proliferation of mammalian kidney mesangial cells would be useful, as it is an important part of the repair process after injury (see Schocklmann, particularly pp. 1199 - 1200 for more detailed discussion). But since the threshold used by applicant was 71% of a change shown not to be statistically significant, one of skill in the art would conclude that the PRO4380 does not induce any more mesangial cells than are induced under control conditions.

The citation of *In re Irons* is also not relevant to the instant case. In *Irons*, evidence was submitted that indicated that the drug had been administered to 888 patients and that

statistically significant results were obtained showing an improvement in arthritic conditions. In the instant case, no such evidence has been submitted. In the instant case, the claimed product has not been administered to patients. Furthermore, there is no evidence of record indicating a statistically significant result in vitro.

The *Sichert* court ruled that blind comparative studies of the claimed compositions, which showed that the compositions were effective in relieving lymphatic congestion (as narrowly defined), were sufficient to establish utility of said compositions under 35 USC § 101. In the instant case, applicant has not shown any such studies, and therefore because the fact pattern is sufficiently different the *Sichert* case is not germane.

In *Raytheon v. Roper*, utility was found by the Federal Circuit when a lack of utility had been found by a lower court. This was due not to the sufficiency of the evidence presented, but rather because the Federal Circuit ruled that the claims in question had been interpreted erroneously. In the instant case, there does not appear to be a question as to how the pending claims are being interpreted.

It is not immediately apparent why applicant has cited *In re Oetiker* in arguments related to the utility under 35 USC § 101, as the *Oetiker* case dealt not with utility but with obviousness under 35 USC § 103. No claims have been rejected under § 103 in the instant case.

The examiner acknowledges that the ability to induce mesangial cell proliferation is specific. However, the assay used by applicant and reported in Example 41 beginning on p. 168 of the specification would not allow a skilled artisan to conclude that it is more likely than not that the asserted utility is true and therefore the asserted utility is not substantial.

On p. 8 of the remarks applicant discusses the examiner's interpretation of the results from Rovin. The examiner and applicant appear to agree on this point. Rovin clearly stated that the data point, a 21% increase, did not represent a significant difference due to the large degree of variability inherent in this assay. Because of the large degree of error, a 21% increase is not significant. Stated another way, one of skill in the art would recognize that it is *improper* to conclude that the two samples (control and 5 uM ciglitazone) are drawn from different populations.

Significance does not mean, as applicant asserts on p. 8 of the remarks, that there is not an overlap of standard deviations or errors in the data set. Rather, statistical significance is a determination, based on mathematic procedures, that the observed difference between samples has a less than 5% chance of occurring by random accident (see attached definition from the

On-line Medical Dictionary, accessed 22 July 2005). Applicant argues that Rovin's report of a 21% non-significant difference indicates that the statistical error in their measurement overlaps with the statistical error in the control set, and that "this does not mean that an increase of proliferation of 21% is not scientifically important or significant, but means that Rovin's particular measurement of 21% may be incorrect due to the amount of error for that data point." This is not the way significance is understood in the art. Significance is an inference. When a result reaches statistical significance, it is proper to infer that the two samples are drawn from separate populations. When the result is not significant, the appropriate inference is not that the particular value is subject to error, but rather that it is not possible to tell if the two samples were drawn from separate populations. Applicant is directed to the attached text from the chapter by Freund et al. (2003. Statistical Methods, Second Edition, pp. 117 – 138), particularly the definition of "significance level" on p. 126 and the definition of "p value" on p. 133 for a more complete understanding of the way statistics are used in scientific papers. In the instant case, Rovin et al. used analyses of variance, followed by post-hoc Bonferroni-corrected pairwise comparisons (see p. 1295, second column "Statistical Analysis") rather than the standard argued by applicant. The teachings of Rovin indicate that this assay has so much variability that even if a 21% difference is detected when 12 experimental and 12 control samples are provided (see legend for Figure 2 which indicates that "[e]ach point represents the mean of at least 3 individual experiments done in quadruplicate".

On p. 9 of the remarks, applicant points out that Rovin found an 18% increase was significant. Applicant again asserts his own definition of significance (p. 12, second paragraph) which contradicts that provided on p. 1295 of Rovin. It is noted that this level is still greater than the changes reported in the specification, where only a 15% increase is considered important. However, taken with the finding that a 21% increase in this assay is not significant, this finding further supports the examiner's point that knowing the variability associated with the measurements is crucial to determining whether or not the artisan will conclude that samples are drawn from different populations. In the instant case, the specification does not disclose the variability in the sample, so a skilled artisan would not reasonably conclude that PRO4380 induces mesangial cell proliferation. Neither PRO4380 nor antibodies which bind to it are useful. Thus the rejection under 35 USC § 101 stands.

8. Claims 22 – 26 and 28 – 30 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

***Claim Rejections - 35 USC § 102***

9. Claims 22 – 25 and new claims 28 – 29 are rejected under 35 U.S.C. 102(a) as being anticipated by Ruben et al. (WO 99/58660, published 18 November 1999) as evidenced by Harlow et al. (1988. Antibodies: A Laboratory Manual) for the reasons made of record in the previous office action and reiterated herein. Ruben et al. teach specific preferred epitopes along the entire length of the protein which can be used for the production of antibodies (see p. 49, lines 17 – 20). Ruben et al. further teach that their antibodies include monoclonal antibodies, Fab and F(ab')2 fragments, chimeric, single-chain, and humanized antibodies (see paragraph spanning pp. 196 – 197). As detailed in the previous office action, the antibodies from Ruben would be expected to bind to SEQ ID NO:57, and Harlow provides evidence of such.

On page 10 of the remarks applicant refers to the declaration by Goddard et al. as providing support for the argument that the 102 rejection should be withdrawn because applicant possessed the claimed invention before the reference was published. The declaration filed on 20 June 2005 under 37 CFR 1.131 has been considered but is ineffective to overcome the Ruben reference. The evidence submitted is insufficient to establish a reduction to practice of the invention in this country or a NAFTA or WTO member country prior to the effective date of the Ruben reference.

Paragraph 5 of the declaration by Goddard et al. indicates that applicant was in possession of the protein with SEQ ID NO:57 before the date of the Ruben reference. Paragraph 8 of the declaration indicates that applicant reduced the protein to practice prior to the date of the Ruben reference. The instantly-claimed invention is an antibody, not a protein. The declaration submitted does not provide evidence of reducing the antibody to practice before the date of the Ruben reference. Therefore the reference is not sufficient to overcome the rejection of claims 22 – 25.

***Claim Rejections - 35 USC § 103***

10. Claims 22, 25, 26, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruben in view of Holmes et al. (Current Protocols in Immunology, cited in previous office

action). Ruben et al. teach antibodies which bind to SEQ ID NO:57. Ruben et al. do not teach a labeled antibody. Holmes et al. teach conjugation of multiple labels (FITC, biotin, Texas Red, and phycobilipoproteins) to antibodies for detection. It would have been obvious to one of ordinary skill in the art to label either the antibodies or the fragments from Ruben, as taught by Homes, with a reasonable expectation of success. The motivation to do so would be to detect the antibodies or fragments, as Holmes teaches that labeling is useful for quantification of the antigen to which the antibody binds, and can be done with antibodies in general.

On page 12 of the remarks applicant refers to the declaration by Goddard et al. as providing support for the argument that the 103 rejection should be withdrawn because applicant possessed the claimed invention before the reference was published. The declaration filed on 20 June 2005 under 37 CFR 1.131 has been considered but is ineffective to overcome the Ruben reference. The evidence submitted is insufficient to establish a reduction to practice of the invention in this country or a NAFTA or WTO member country prior to the effective date of the Ruben reference.

Paragraph 5 of the declaration by Goddard et al. indicates that applicant was in possession of the protein with SEQ ID NO:57 before the date of the Ruben reference. Paragraph 8 of the declaration indicates that applicant reduced the protein to practice prior to the date of the Ruben reference. The instantly-claimed invention is an antibody, not a protein. The declaration submitted does not provide evidence of reducing the antibody to practice before the date of the Ruben reference. Therefore the declaration is not sufficient to overcome the rejection of claims 22 and 25, as explained in the rejection under 35 USC 102 above. The declarations is also not sufficient to overcome the rejection of claims 26 and 30, as it would still be obvious to label the antibodies and fragments. Applicant did not traverse the examiner's rejection of obviousness and since the declaration is not sufficient to overcome the reference the rejection stands.

***Rejections Necessitated by Amendment***

***Claim Rejections - 35 USC § 102***

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 25, 28, and 29 are rejected under 35 U.S.C. 102(a) as being anticipated by Ruben et al. (WO 99/58660, published 18 November 1999) as evidenced by Harlow et al. (1988. Antibodies: A Laboratory Manual). The reasons why claim stands rejected is explained in detail above in the section under Rejections Maintained. Briefly, Ruben teaches a sequence very similar to instantly-claimed SEQ ID NO:57, and Harlow provides evidence that the antibody from Ruben would be expected to bind to applicant's SEQ ID NO:57. New claims 28 – 29 are also rejected because Ruben defines "monoclonal antibody" as including antibody fragments, and also includes humanized antibodies within the scope of this definition, thereby meeting the limitation of claims 28 – 29 (see Ruben pp. 196 – 197).

### *New Rejections and Objections*

### *Oath/Declaration*

12. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration, particularly the changes to citizenship by Zhang and to address by Eaton. See 37 CFR 1.52(c).

### *Claim Rejections - 35 USC § 102*

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 22 – 25 and 28 – 29 are rejected under 35 U.S.C. 102(e) as anticipated by Ruben et al. (U.S. Patent application publication 2003/0100051, published 29 May 2003, filed 10 September 2001, claiming priority to applications filed 28 June 2001, 10 November 1999, 6

May 1999, and claiming benefit of provisional applications filed 11 September 2000, 18 May 1998, and 12 May 1998), as evidenced by Harlow et al. (cited in previous office action).

Ruben et al. teach SEQ ID NOs:137, 139, and 242, each of which are 97.0% identical to applicant's SEQ ID NO:57 (see attached alignments). Ruben's sequences are identical to applicant's SEQ ID NO:57 from residues 16 – 507 (using applicant's residue numbers). Ruben teaches antibodies to these sequences, including both monoclonal and humanized antibodies as well as Fab fragments, F(ab') fragments, and fragments produced by a Fab expression library (see page 116, paragraph 0796). Although the polypeptide sequence of Ruben et al. is not identical to that of SEQ ID NO:57, the two are so close that it is expected that an antibody raised against either one would recognize the other. The teachings of Harlow et al. are particularly informative. Page 76 of Harlow indicates that long peptides, including the hydrophilic regions, are likely to produce antibodies and that sequences as short as six amino acid residues can be immunogenic. Clearly the high degree of identity between the two peptide sequences, and the fact that the hydrophobic region identified by applicant as the transmembrane domain is identical in both, indicates that the antibodies produced by Ruben et al. will recognize the polypeptide of SEQ ID NO:57. The prior art teachings of Ruben et al. therefore meet the limitations of claims 22 – 25 and 28 - 29.

It is acknowledged that applicant's declaration under 37 CFR 1.131 is sufficient to indicate that he was in possession of the claimed material prior to 18 November 1999. However the publication by Ruben cited herein claims benefit of provisional applications filed 12 May 1998 and 18 May 1998. These are the same applications cited on the face of WO 99/58660, which was the basis of the rejection under 35 USC 102 (a) in the previous office action.

***Claim Rejections - 35 USC § 103***

15. Claims 22, 25, 26, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruben et al. (U.S. Patent application publication 2003/0100051, published 29 May 2003, filed 10 September 2001, claiming priority to applications filed 28 June 2001, 10 November 1999, 6 May 1999, and claiming benefit of provisional applications filed 11 September 2000, 18 May 1998, and 12 May 1998) in view of Holmes et al (1995. Current Protocols in Immunology, pp. 5.3.5 – 5.3.8). Ruben et al. teach antibodies which bind to SEQ ID NO:57 and fragments of the antibodies, as explained above. Ruben et al. do not teach a labeled antibody. Holmes et al. teach conjugation of multiple labels (FITC, biotin, Texas Red, and phycobilipoproteins) to

antibodies for detection. It would have been obvious to one of ordinary skill in the art to label the antibodies or antibody fragments of Ruben et al. for purposes of detecting PRO4380, using one of the protocols provided by Holmes et al., with a reasonable expectation of success. A motivation for doing so would be to label a cell or cells that express PRO4380, and Holmes teaches preferred methods for labeling as recognized by the skilled artisan.

***Conclusion***

16. No claim is allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHARON TURNER, PH.D.
PRIMARY EXAMINER
8-18-05

Daniel E. Kolker, Ph.D.
August 16, 2005